Topical Review: New Insights into the Pathology and Diagnosis of Disorders of the Temporomandibular Joint

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The collection of conditions affecting the temporomandibular joint (TMJ) and masticatory muscles, the so-called temporomandibular disorders, can be classified according to the Research Diagnostic Criteria for Temporomandibular Disorders. Of the 3 subgroups—muscle disorders (Group I); disc displacements (Group II); and arthralgia, arthritis, and arthrosis (Group III)—the muscle disorders are most frequently seen in community samples; Group II and Group III diagnoses are less prevalent. This may explain the relative scarcity of studies involving intracapsular TMJ disorders. In this review, new insights into the functional anatomy, imaging, and pathology of disorders of the TMJ are presented. Studies of TMJ dynamics may provide insight into the functional anatomy of the TMJ and thereby into the consequences of Group II and Group III disorders. The clinical use of imaging modalities such as computed tomography and magnetic resonance imaging for the TMJ and related structures remains controversial. Nevertheless, imaging is regularly used in the diagnosis of some Group II and Group III disorders. Magnetic resonance imaging may be of use not only for the visualization of disc displacements but also for the study of bone mineral density of the condyle. Cytokines such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNFα) play an important role in TMJ pathology. For example, IL-1β, which has been associated with TMJ pain, hyperalgesia, and anterior bite opening, is mostly absent in the synovial fluid of healthy joints. Since both IL-1 and TNFα are involved in the development of chronic pain and joint destruction, they may be the targets for specific treatments. While the advances reviewed in this paper are significant, multidisciplinary efforts and formation of international research collaborations will be necessary to continue advancement in the understanding of TMJ pathology and diagnosis. J OROFAC PAIN 2004;18:181–191

Key words: cytokines, imaging, functional anatomy, temporomandibular disorders, temporomandibular joint

This review is based on a symposium titled "New Insights Into the Pathology and Diagnosis of Disorders of the TMJ" presented at the annual meeting of the International Association for Dental Research in Chiba, Japan, in June 2001.

Subgroups of temporomandibular disorders (TMD) in which the temporomandibular joint (TMJ) is involved have been considered for at least 20 years to be distinct subtypes of TMD. However, several different classification systems, including the Helkimo Index, TMJ scale, and Craniomandibular Index, among others, have categorized these subtypes in different fashions.[1] In 1991, an international group of TMD investigators developed a diagnostic system with specific operational criteria and specifications to diagnose and study TMD. This system, called the Research

Table 1 Prevalence of TMD Among Clinical and Community Cases Grouped According to the RDC/TMD

Diagnosis	Prevalence (%)	
	Clinical	Community
Group I	12	25
Group II	9	3
Group III	6	4
Groups I and II	8	8
Groups I and III	35	22
Groups II and III	1	2
Groups I, II, and III	18	8
No RDC diagnosis	12	28

Adapted from Le Resche.[3]
Group I = muscle disorders; Group II = disc displacements; Group III = arthralgia, arthritis, arthrosis; RDC/TMD = Research Diagnosis Criteria for Temporomandibular Disorders.

Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD), has 2 main axes of diagnosis: Axis I, the clinical TMD diagnosis, and Axis II, the psychosocial status of the person.[2] Algorithms were developed to combine historical and examination data into specific TMD subtype diagnoses. For example, a report of pain in the joint region at rest or with function, along with pain of the TMJ on palpation, leads to the diagnosis of arthralgia. Three main diagnostic subgroups of TMD can thus be distinguished: muscle disorders (Group I); disc displacements (Group II); and arthralgia, arthritis, and arthrosis (Group III). Of these 3 subgroups, the muscle disorders, with or without joint problems, are most prevalent in community-based samples. Group II and Group III diagnoses, which do not involve the masticatory muscles, are less common. This may explain the relative scarcity of studies involving arthrogenous TMJ disorders. Group II and Group III diagnoses are the main focus of this review. The authors present an overview of the current scientific literature on the epidemiology of disc displacement and arthralgia, including the frequency, natural history, risk factors, and causal models, followed by new insights into the functional anatomy, imaging, and pathology of disorders of the TMJ.

Epidemiology

Population-based estimates of the prevalence of TMD among community cases show that diagnoses of Group II only (disc displacements) or Group III only (arthralgia, arthritis, arthrosis) are relatively uncommon (Table 1). However, these conditions are commonly diagnosed in conjunction with other subgroups (Table 1).[3] Studies of the incidence of subgroups of TMD show an increased incidence in the early teens for Group II disorders (about 3 per 100 person-years).[4] Incidence studies of Group III disorders show an increased incidence of arthritis and arthrosis among those older than 60 years of age.[5] These epidemiologic studies show that any general theory of the etiology of TMD must account for *(1)* the low prevalence in children; *(2)* the apparent higher incidence (new cases) in adolescence; *(3)* the higher prevalence among women; *(4)* the low prevalence among the elderly; and *(5)* the intermittent nature of these disorders.

Few studies of the natural history of TMD subtypes exist. The natural history of any type of TMD pain reveals different clinical courses that result in the pain resolving, reducing, becoming episodic, or, in a few cases, persisting.[6] The natural history can be best predicted by baseline measures of depression and somatization and not by clinical measures such as range of motion, type of disc displacement, or TMD subgroup.[6] People with TMD disc displacement exhibit the condition intermittently.[4]

The literature on the analytic epidemiologic study of the risk factors for any type of TMD is still in its infancy, and few studies about Group II or Group III disorders only are available. Many of the published studies on this topic suffer from methodological problems. For example, a systematic review of TMD risk factors considered more than 90% of the studies ineligible because they failed *(1)* to use self-reported pain in the case definition and *(2)* to control for the potentially confounding effects of age and gender.[1,7] Studies of overall TMD pain show that multiple pre-existing pain conditions, female gender, self-reported sleep bruxism, and depression are associated with the onset of TMD pain.[7] Of the few risk factor studies of TMD subgroups, several case-control studies have shown moderate associations between joint laxity and Group II disorders[8] and between loss of posterior support and the risk of Group III disorders.[9] A recent case-control study of TMD subgroups showed that somatization, tooth clenching, third molar removal, and trauma were risk factors for the myalgia-only and myalgia/arthralgia subgroups.[10] Although there were only 20 cases in the arthralgia-only subgroup, the associations with each risk factor were similar to those found for the myalgia and myalgia/arthralgia subgroups, with the exception that trauma was not a risk factor for arthralgia only. This study hints that differentiating between TMD subtypes in etiological studies

may not yield substantially different risk factors than those for TMD of all types. However, more epidemiological studies are needed to characterize better these subgroups of TMD. The optimal study design to investigate the risk factors of TMD subgroups is the case-control study because of the relative rarity of these patients.[1]

Analysis of analytic epidemiologic studies without an idea of the possible causal pathways is prone to error. Whether a variable is an exposure (risk factor), confounder (nuisance variable), intermediate, effect modifier (synergistic variable), or outcome (disease variable) should be determined before the study begins and evaluated in an iterative process during the analytic phase of a study. Causal diagrams, also known as directed acyclic graphs, have been developed that can quantitatively show the relationships between these variables.[11] The directionality and temporal sequence are included in these models, which adds heuristic value to them. It is critical to understand what category a variable fits into before attempting to analyze the data; otherwise, a variable may be controlled that should not be, or vice versa. An illustrative example is as follows: a risk factor and exposure for TMD pain is depression which, through sleep interruption, may lead to increased sleep bruxism, which would be an intermediate variable. This sleep bruxism, in turn, may contribute to TMJ arthralgia. If a person is given a selective serotonin reuptake inhibitor to treat the depression, it may attenuate the depression but contribute to further bruxism.[12] In this case, the depression medication may serve as a confounder, which would call for controlling for it in the analyses, or as an effect modifier, in which case this possible synergism should be elucidated through stratified analyses. This example shows that the apparent association between depression and TMD pain could actually be spurious and is instead related to the medications that are commonly used to treat depression. TMD risk factor studies have yet to fully take into account these important exposures, modifiers, and outcome variables.

Substantial progress has been made in our understanding of the epidemiology of TMD and its subtypes in the past 15 years, but much more work remains to be done. Unexplored risk factors, such as adverse early life events, physical activity, obesity, beliefs and coping strategies, and mild traumatic brain injury, among others, all await further study. Proper use of epidemiologic methods in future studies will likely result in a greater understanding of the causes and possible prevention of TMD pain and its subtypes.

Functional Anatomy

The functional interactions within the TMJ are not completely understood, which has resulted in questionable assertions regarding structure-function associations. This speculation about, rather than demonstration of, articular biomechanics has led to erroneous conclusions of cause-effect relationships, some of which may adversely affect the assessment, diagnosis, and management of functional disorders. The negative effect of such speculation is most vividly illustrated by the example of unsuccessful alloplastic TMJ disc implants.[13] Their catastrophic failure exemplifies the need to understand the biomechanics of this musculoskeletal system and the subsequent relevance of functional anatomy in the predisposition, onset, and perpetuation of TMD. Importantly, since articular function is derived from the interaction of various soft and hard tissue constraints (eg, muscle activity, dental contacts, articular morphology), its analysis must include a consideration of masticatory system biomechanics in toto.

Many varied methods have been used to examine the functional anatomy of the TMJ, including numerous primate and nonprimate animal studies. Animal studies are advantageous in that invasive structural and functional procedures are possible and provide important insight into TMJ biomechanics, such as functional articular compression,[14] the constraining role of TMJ ligaments,[15] and remodeling and disc damage with appliance use.[16] However, caution must be exercised in extrapolating these findings to humans because of the morphologic and functional differences between humans and animals.

In humans, in vivo approaches include the simple but clinically relevant measurement of incisor displacement as well as experimental measurement of bite force and muscle activity. An additional approach is the comprehensive assessment of jaw motion from which condylar motion can be approximated or, in the best case, can be accurately determined when motion is matched with joint morphology.[17,18] This latter scenario is ideal but requires matched 3-dimensional imaging, motion acquisition, and sophisticated data manipulation. Dynamic magnetic resonance imaging (MRI) has recently been used for direct in vivo investigation of articular function and shows much promise as a noninvasive method of disc function assessment.[19] The lengthy acquisition time is a drawback because it limits the recording of jaw movements to those occurring at much slower rates than in normal function; however, this limitation

should diminish with continuing technological advances in the imaging field.

Since the measurement of many anatomic and functional properties such as joint forces, jaw muscle tensions, joint capsule attachments, and muscle fiber lengths in humans is impossible or impractical, static and dynamic mathematical models have been used to estimate these unknowns. These models can predict outcomes and can easily be adapted to new functional and structural input as more information becomes available.

The more complex static models divide anatomic structures into thousands of finite elements with assigned physical properties.[20] One of the more recent finite element models was derived from a cadaver specimen and consisted of an independent condyle, disc, and fossa.[21] In this model, articular mechanics were derived by displacing the condyle toward the disc and fossa at simulated closed, hinged-open, protruded, and open positions. Compared to the closed position, the hinged-open position demonstrated increased strain in the 3 joint components. At the protrusive and opening positions, deformation occurred in the lateral articular region, and the joint contact area was smaller when the condyle and disc were on or near the eminence than when they were in the fossa. In addition, this finite element model of the disc was evaluated against in vitro specimen loading. The interactions between the collagen/proteoglycan matrix and interstitial fluid could be simulated with a poroelastic model, ie, when the disc was cyclically loaded, and it demonstrated time-dependent physical properties such that reaction forces and energy dissipation decreased in time. Thus, with repeated loading, compressive joint forces may concentrate locally in the disc, rather than being distributed through it. Together with findings of increased frictional changes with impulse loading,[22] this has important functional consequences.

To address the controversy surrounding the role of the capsule (including temporomandibular ligaments) in jaw function,[23] kinematic models, which analyze motion without regard to the driving forces, have been developed.[24] For typical mandibular border movements, these models assessed length changes between putative ligament attachments on the temporal bone and condylar neck. A lateral capsular wall of 12,000 linear elements between these attachment points was constructed. Any part of this wall that remained taut (defined as remaining within 5% of maximum length) throughout mandibular movement was considered an articular constraint. Throughout ipsilateral movements, there were taut elements between the anterosuperior region of the eminence and the posteroinferior aspect of the condylar neck. However, throughout opening, protrusive, and contralateral motions, taut elements were found only during the initial third of movement and at the limit of motion. The lack of taut capsular regions during the middle third of these movements (presumably a major functional region of the joint during mastication) suggests that other variables are responsible for maintaining apposition of articular structures in function.

Kinetic, muscle-driven models have been created in an attempt to simulate plausible jaw behavior.[25] Commercial software (eg, ADAMS, MDI, Michigan) has been used to develop mathematical models that predict dynamic solutions based on the model's previous history with numerical integration methods. The best available structural and functional data, such as the mass properties of the jaw (eg, mass, moments of inertia) which are often estimated indirectly, are put into the model. These are necessary inputs since they provide resistance to linear and angular accelerations, respectively. They are derived from a body's geometry and mass distribution.[26] Valid estimates of jaw behavior have been recently derived from imaging and even more simply from calculations based on the mandibular length (ie, the distance between the condylion and the gnathion).[27] The magnitudes of the passive muscle tensions that resist jaw movement, which include elastic and viscous properties, are unknown. It appears that the maintenance of wide mouth opening in relaxed subjects requires relatively low forces, in the range of 5 to 10 N.[28] Viscosity of the jaw, which has been estimated by varying the rate of opening with a force gauge applied to the lower incisors, most probably plays a role in maintaining jaw stability.[29] Articular stability and jaw posture may also be enhanced by thixotropy, a property found in other joints in the body, whereby stiffness increases with inactivity and decreases with activity.[29]

The masseter, medial pterygoid, and temporalis are all structurally complex,[30] and recent research suggests that the "straplike" lateral pterygoid is functionally heterogeneous and thus is not as simple as previously thought.[31] This complexity has been explored with a multilayered masseter model that simulates jaw opening.[24] Structural and functional properties were derived from previous human and animal experimentation.[32–34] During stretch, the 5 tendinous aponeuroses demonstrated sliding and twisting behavior that minimized passive tension generation in the muscle. This concurs with the low passive tension observed in the jaw

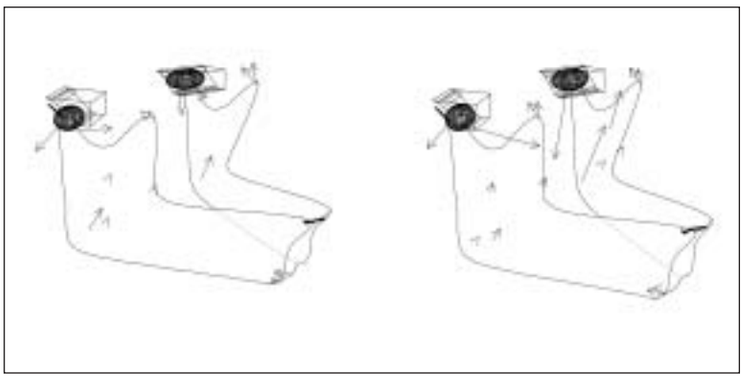

Fig 1 Simulated lateral jaw motion (with tooth contact) obtained by different muscle activation strategies (left and right figures). Anterolateral view of jaw model including muscle vectors at extreme lateral position. Bold lines represent mandibular incisor and condylar pathways. Calibration bar = 10 N (force vectors) or 10 mm (incisal/condylar displacement).

during opening. With whole jaw modeling, however, it is not feasible to model the structural and functional complexity of the masticatory muscles because of the difficulty in reconstructing their detail and the computational cost incurred in simulating function. Instead, the muscles can be "black-boxed" and represented by single straight-line force vectors with realistic passive and active tension properties. Further simplifications include modeling the TMJ as an ellipsoidal condyle apposed to a curvilinear disc-fossa boundary, with physical properties derived from extracranial fibrocartilaginous tissue.[28]

With this jaw model, plausible lateral motion, as measured at the incisor point and condyles, was possible with different, yet realistic, muscle activation strategies (Fig 1).[24] Notably, condylar reaction forces could be reversed, which suggests that joint loading in patients may be altered in a predictable fashion by retraining muscle behavior.

Recently, this jaw model has been used to predict dynamic changes in articular and occlusal forces during simulated tooth clenching.[35,36] The dentition in the model was modified to include multiple cuspal facets to simulate a stable Angle's Class I malocclusion (intercuspation), an anterior open bite and a posterior open bite. Dynamic clenching was simulated by uniform increases in temporalis, masseter, and medial pterygoid activity to reach maximum muscle tensions in 0.5 seconds. In the Class I model, articular loads increased rapidly to reach near maximum values (150 to 170 N) at 50% of the maximum muscle tension. In contrast, the anterior and posterior open-bite models were unstable. They produced greater articular loads that increased progressively throughout the clenching task to reach maxima of 400 to 800 N. These predicted high TMJ forces in open-bite occlusions are unlikely to occur in vivo where decreased and/or differential muscle contraction might be expected. However, as more accurate structural and functional data are acquired, they can be simply included in the model. These models are useful in refining hypotheses to drive clinical experimentation and offer a new method to investigate the complex interactions between the variables that affect the functional anatomy of the TMJ.

Imaging

Clinically, imaging of the TMJ is frequently used to screen for unexpected pathology, to confirm the presence of RDC/TMD Group II and Group III disorders, and to identify the progression of a disease.[37] Ongoing developments in imaging leave the clinician with an ever-growing choice of techniques. A representative development in TMJ imaging is the detection of disc displacements with MRI. However, disc displacements are also seen on MRI of about a third of asymptomatic volunteers,[38] which raises questions about the specificity of this test and its applicability for diagnostic purposes. Similarly, although conventional radiographs have played an important role in the diagnosis of osteoarthritis/osteoarthrosis (OA) in the TMJ as well as in other body joints until now, there is only a limited correlation between clinical and radiographic findings for TMJ OA.[9] This correlation is limited not only by limitations of the imaging technique but also by the clinical assessment criteria. Studies of TMJ OA are difficult: Because of its low prevalence, approximately 8% among TMD patients,[39] large population samples are required. Furthermore, there is a lack of population studies specifically focused on TMJ OA. In the only known large-scale study on this topic, Sato et al[9] showed that in a population of more than 600 Swedish individuals 70 years of age, 26% presented abnormal radiographic findings in 1 (18%) or both (8%) TMJ(s), while both clinical and radiographic findings were abnormal in only 5% of the cases.

MRI can detect not only TMJ soft tissue abnormalities such as disc displacements but also hard tissue morphologic abnormalities of the mandibular condyles. In addition, bone marrow signal changes in relation to TMJ OA can now be demonstrated with MRI.[40,41] Lieberman et al[40] and Larheim et al[41] classified the MRI signal pattern of the bone marrow of the mandibular condyle into normal, edema, or osteonecrosis categories. The osteonecrosis category was further subdivided into a sclerosis pattern and a combined sclerosis and edema pattern. It is possible that MRI-determined bone marrow abnormalities are manifestations of TMJ OA. However, the cause, its clinical significance, and the need for treatment are still uncertain. Since these findings regarding the mandibular condyle were slightly different from those regarding the femoral head,[40] confusion remains.

Like MRI, computed tomography (CT) is able to evaluate not only abnormal morphologic changes of the TMJ but also bone mineral density (BMD) of the mandibular condyle. Yamada et al[42] measured the trabecular mandibular condyle BMD by means of CT and showed that, like BMD in other body joints, mandibular condyle BMD regressed with increasing age. A close relationship between BMD and general body factors, such as age and the amount of muscle force, has been suggested in the literature.[43] A positive significant relation between mandibular condyle BMD and bite force was found in young men but not in young women.[42] In a group of about 70 postmenopausal women, multiple regression analysis showed, after the elimination of the age factor, that bite force and the number of residual teeth were significantly correlated with trabecular mandibular condyle BMD.[44] The importance of functional loading and dental state for mandibular condyle BMD might be supported by these results.[44]

Such MRI and BMD evaluations of bone marrow signal changes and of mandibular condyle trabecular BMD differ from assessments of predominantly morphologic changes by previous imaging modalities, thus enabling a more complete evaluation of both the structural framework and the composition of the TMJ. Therefore, once the clinical interpretation, reliability, and validity of these image-derived outcomes have been established, TMJ pathology may be detected at an earlier stage than is presently possible.

Useful information about the pathology and normal features of the TMJ is still scarce. Therefore, more studies are necessary on the relationships between TMJ imaging, anatomy, and function using not only human subjects but also animals.

Inflammatory Mediators

One of the problems in the diagnosis of disorders in the TMJ is accurate determination of whether there is an active inflammatory process and whether this process is of a destructive nature. A second problem is how to predict future tissue destruction or the progression of destruction. A third problem is how to identify specific targets for treatment of TMJ pain and destruction due to this inflammation.

This review will focus on rheumatoid arthritis (RA), which is an inflammatory connective tissue disease (collagenosis) of systemic character. The disease can involve any joint in the body, including the TMJ, but usually starts in the peripheral joints such as the finger and toe joints and eventually spreads proximally to involve large joints such as the knee and shoulder joints. The extent of the joint involvement and the severity of the inflammatory process vary considerably, but the disease often follows a chronic course with slow, progressive destruction of joint cartilage, bone, and other joint tissues. According to several clinical studies, about 1 in every 2 or 3 patients with RA can be expected to experience symptoms in the TMJ.[45]

The cause of RA is still largely unknown, but there is evidence indicating that immunologic and neural mechanisms are involved and interact. The rheumatoid process starts as an inflammatory reaction in the synovial membrane (synovitis) and surrounding connective tissue. The synovial membrane is transformed into a hyperplastic and granulomatous tissue (ie, tissue rich in blood vessels) by the release of cytokines. This tissue grows invasively over the joint surfaces and may cause destruction of the bone cortex and then also of bone. Cytokines, among them tumor necrosis factor alpha (TNFα) and interleukin 1 (IL-1β), participate in the development of the rheumatoid process by activating lymphocytes and stimulating prostaglandin and collagenase production as well as cartilage resorption and muscle breakdown. This section will concentrate on the effects of these 2 cytokines.

Both TNFα and IL-1β are mainly derived from macrophages and play a key role in the amplification and perpetuation of inflammation in several conditions besides RA.[46] Antigen presentation in the joint tissues by macrophages expressing the genetic factor HLA-DR 1/4 appears to play an important role in the development of arthritis. Interaction in the synovial membrane between the antigen-presenting cell and specific receptors on the surfaces of T-cells activates the T-cells to produce

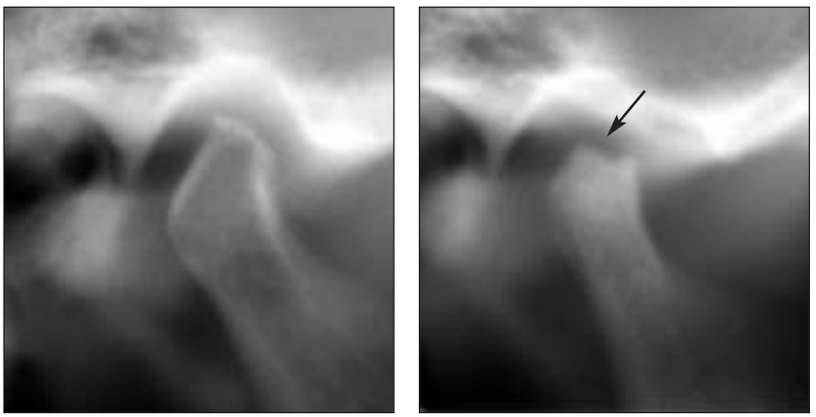

Fig 2 Progression of radiographic erosion in the temporomandibular condyle from 1993 *(left)* to 1998 *(right)* in a patient with seropositive RA. In 1993, there was no erosion of the condyle, P-IL-1β = 8.2 pg/mL; In 1994, P-IL-1β = 8.1 pg/mL; and in 1998, extensive erosion of the condyle was evident *(arrow)*, and P-IL-1β = 0.0 pg/mL.

cytokines including IL-15, and an inflammatory reaction results. Following antigen recognition, the presenting macrophage and polymorphonuclear cells secrete TNFα, which stimulates synovial and endothelial cells as well as macrophages and hepatocytes to release IL-1β, IL-6, prostaglandins, and acute phase proteins (eg, C-reactive protein [CRP]).[47] The IL-1β then induces several inflammatory events, ie, it activates lymphocytes, it stimulates prostaglandin and collagenase production in connective tissue cells, and it stimulates cartilage proteoglycan breakdown. It is known that TNFα and IL-1β mediate cartilage destruction by stimulating chondrocytes to produce proteinases, eg, matrix metalloproteases, and possibly oxidative radicals.[48] Furthermore, IL-1β blocks the synthesis of proteoglycans and collagen type 2 by chondrocytes.

The appearance of TNFα in the synovial fluid (SF) of the TMJ is associated with local joint pain and tenderness to palpation. Also, TNFα in plasma is associated with TMJ pain.[49]

The presence of IL-1β is seldom detectable in the SF of the TMJ from healthy individuals, whereas patients with polyarthritides have significant SF concentrations of IL-1β in the TMJ.[50] The IL-1β found in the SF of the TMJ from patients with inflammatory disorder seems to originate from local production rather than from the plasma, since the correlation between the two is poor and the level of IL-1β is much higher in the SF than in the plasma in these patients. In recent investigations it has been found that there are significant positive correlations between the amount of IL-1β in the SF of patients with arthritic TMJs and pain and tenderness to digital palpation as well as a negative correlation to pressure pain tolerance level.[51] It therefore seems that IL-1β is 1 of the determinants of pain, allodynia, and hyperalgesia of the TMJ.

The level of IL-1β in the SF has also been found to be related to radiographic signs of TMJ destruction.[52] Radiographic change such as erosion of the cortical outlining is a common finding in RA patients. The extension of radiographic erosion has been found to be significantly greater in joints with IL-1β than in those without.

An important question is whether inflammatory mediators or markers in the blood or SF of the TMJ could predict the progression of TMJ destruction. So far, progression of bone loss in the arthritic TMJ has been found to be associated with raised levels of CRP and IL-1β in plasma (Fig 2).[53]

Of the many cytokines present in the SF of patients with RA, TNFα and IL-1β are assumed to have particular importance in the inflammatory disease process, and the blocking of production of TNFα has been introduced as a new therapeutic approach.[54] Monoclonal anti-TNF antibodies were shown to attenuate collagen-induced arthritis in mice.[55] In preliminary clinical trials including patients with RA, anti-TNF antibodies appear to have a significant effect on disease activity including reduced CRP and serum amyloid-A production.[56] Therefore TNFα seems to be a therapeutic target of choice in patients with RA. Administration of soluble TNFα receptor (p75, etanercept [Enbrel; Immunex]) has also shown promising results in the treatment of RA.

Infliximab (Remicade; Centocor) is a chimeric monoclonal antibody (cA2, which binds to TNFα and thereby neutralizes its biologic actions, eg, by reduction of CRP release). According to the preliminary results of 1 of the authors (SK), infliximab results in a significant reduction of both general joint pain as well as local TMJ and knee joint pain within 2 weeks (Fig 3). The pain reduction was associated with decreased levels of IL-6 in the SF.

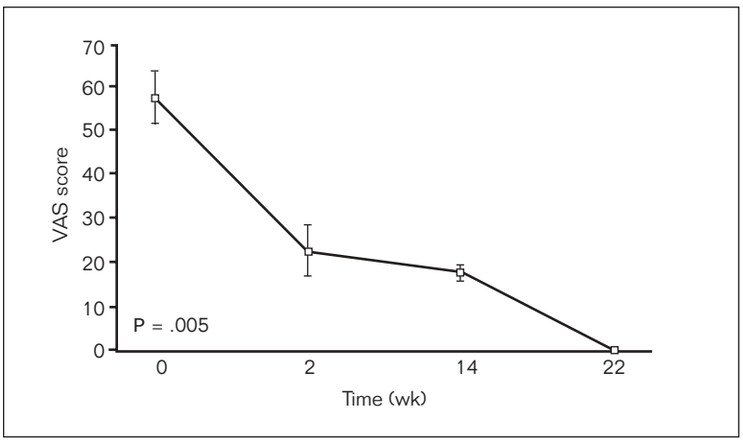

Fig 3a General joint pain (mean ± standard deviation) in 5 patients with RA after infusion with infliximab according to a visual analog scale from 0 to 100 mm. Pain was scored at visits for examinations and infusions.

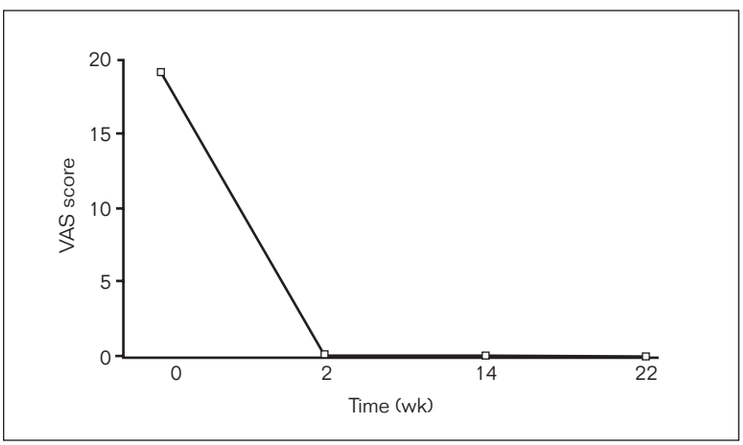

Fig 3b Pain from the right TMJ in 1 patient with RA after infusion with infliximab according to a visual analog scale in mm.

Further treatment possibilities include the IL-1 receptor antagonist protein, the soluble receptor for IL-1, antibodies against IL-1, diacerein, and eventually gene therapy.

Overview and Future Perspectives

The physiology and pathophysiology of the human TMJ have intrigued both researchers and clinicians for years and will undoubtedly continue to fascinate and challenge us in the future. This has become very clear from this review, which has highlighted current understanding in 4 important fields: epidemiology, functional anatomy, imaging, and inflammatory reactions. Each section has carefully described the significant advances made in the particular field described but has also revealed that the knowledge is far from complete. For patients with persistent disorders of the TMJ, it may be surprising and frustrating that health care providers have not yet reached a consensus on the etiology of these disorders and on how to best assess and visualize articular function and its underlying mechanisms; we have not even considered in this review the diversity in management practices for articular disorders, which certainly adds to the confusion. In many ways, the TMJ exemplifies the extreme physiologic complexity in the orofacial musculoskeletal system, with highly differentiated tissues (eg, synovia, tendons, ligaments, muscles, fibrocartilage, nerves, vessels) and its almost constant participation in multiple motor functions (eg, chewing, talking, swallowing, clenching, smiling, kissing, grimacing). Functional, biologic, and psychologic factors obviously interact and influence each other in the orofacial musculoskeletal system, making it difficult and probably meaningless from a clinical perspective to search for a single causative factor. Although much improved, our current classification systems rely mainly on the assessment of fairly simple symptoms and signs, and the classification of underlying mechanisms has only recently attracted attention in the pain field.[57] In fact, clinically, we may have significant difficulties in distinguishing between articular and myofascial pain (since both types of deep pain are diffuse, tend to spread to larger areas, and are associated with referral of pain),[58] let alone between

pain originating from various components of the TMJ. The development of the RDC/TMD is a pragmatic attempt to address the classification problem, and a number of studies have shown adequate reliability of the clinical test procedures.[59] However, the validity of the RDC/TMD in the diagnosis of, for example, arthralgia has not been established. This will await further studies and careful consideration of the basic features of the TMJ.

Clearly, there is a great need to better understand the normal function, biology, and biomechanics of the TMJ, eg, a determination of the variables that are associated with changes or increases in loading patterns. Such variables might constitute potential microtraumatic stimuli to the tissue and initiate a series of pathophysiologic events eventually leading to pain and degeneration of the joint tissue. The threshold between catabolic and anabolic events is likely to be highly individualized and subject to a number of modifying genetic and functional factors. Thus, it needs to be emphasized that the balance between physiologic and pathophysiologic stimuli has not yet been established. Identification of biological markers of both tissue pathology and nociceptive activity will represent a significant contribution to the current imaging techniques of structural changes. Imaging should preferably not only visualize intracapsular TMJ conditions but also the consequences and processes in the central nociceptive system. Techniques like positron emission tomography and functional MRI have launched a new era in the understanding of the living human brain, and the conditions that influence the nociceptive activity have begun to be examined.[60,61] It is likely that it will be possible in the future to use high-resolution imaging techniques to examine central nociceptive processes and peripheral activity (eg, binding of neuroactive ligands, blood flow changes) and learn more about the problematic TMJ.

Thus, modern research approaches to the TMJ will employ biomedical techniques targeting the genetic, cellular, and molecular mechanisms of the different tissues. Understanding the development and morphogenesis of the TMJ will also be an important prerequisite for understanding pathology in the TMJ. Further insight into mediator mechanisms linked with the pathophysiology is warranted. In addition to some of the cytokines mentioned, eg, TNF-α and IL-1β, other candidates need to be examined. Because of the multitude of biological mediators involved in tissue degradation, inflammatory reactions, and nociceptive activity, it may be useful to establish the relative potency of the mediators in question. This will be a tedious task and will require combinations of molecular, pharmacological, and clinical trials.

More accurate diagnosis and development of more rational interventions and management strategies will be based on an integrated approach to the study of the TMJ. Molecular and physiological mechanisms of TMJ nociception and pain need to be investigated in both in vitro and in vivo assays, but the psychological and biobehavioral aspects also must be taken into consideration as essential modifiers of TMJ pain. Multidisciplinary efforts and the formation of international research collaborations will likely be necessary to continue our advancement in the understanding of TMJ pathology and diagnosis.

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